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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,343	MALLET ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed April 21, 2006. Applicant's response to restriction requirement of March 22, 2006 has been entered. No claims have been amended or cancelled, and no new claims have been added.

Claims 35-67 are pending in the application.

Election/Restrictions

Applicant's election of species, with traverse, of plasmid, a replication-defective lentivirus, a neurotrophic factor, retinal degenerative diseases and a human cell, is acknowledged. Applicant timely traversed the restriction (election) requirement in the Paper filed April 21, 2006.

The traversal is on the ground that the search of all claimed subject matter can be made without undue burden, and that the Examiner has not demonstrated the claimed subject matter does not share a special technical feature.

Applicant's arguments have been fully considered, but not found to be persuasive. Each of the elected species does not share a common utility, and does not share a substantial structural feature essential to that utility; and therefore constitute an improper Markush group, lacking unity of invention (In *re* *>*Harnisch*<, 631 F.2d 716, 206 USPQ 300 (CCPA 1980). Further, each is capable of separate use. For example, a plasmid and a virus are composed of naked DNA and protein coat, respectively. A virus is capable of infection of a cell and a plasmid is not. A lentivirus is an RNA virus, whereas an adenovirus is a DNA virus. A neurotrophic factor is distinct in structure and function from an enzyme. A retinal disease has a distinct etiology from Alzheimers disease, affecting different tissues and a human cell and a rodent cell are derived from separate species of animal. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further the search and examination of the distinct species are not co-extensive. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action

on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 35-67 are currently under examination.

Objections to the Specification/Abstract

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Objections – Duplicate Claims

Applicant is advised that should claim 57 be found allowable, claim 58 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 38-39, 43-46, and 64-67 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass numerous polynucleotide sequences comprising portions or fragments of numerous posttranscriptional regulatory elements that retain functional activity. The specification describes the WPRE element (SEQ ID NO: 1; p. 7), the APP

5'UTR element (SEQ ID NO: 2; p. 8), the tau 3'UTR element (SEQ ID NO: 3; pp. 8-9), and the TH 3'UTR (p. 9). However, the specification provides no examples of functional portions or functional fragments of the disclosed sequences demonstrate that such promoter or regulatory sequences were included in the present invention. The claims therefore embrace numerous nucleotide sequence variants of SEQ ID NOS: 1-4, that retain functional activity in conferring posttranscriptional regulation or RNA transcripts. The claims thus constitute a claimed genus that encompasses variant regulatory sequences that retain the activities of SEQ ID NOS: 1-4, yet to be discovered. Since the specification only discloses a single species for each of the four regulatory elements, the disclosed structural features of said elements do not constitute a substantial portion of the claimed genus. As such, the person skilled in the art could not predict that Applicant possessed any additional species, except for the sequences of SEQ ID NOS: 1-4. Hence, only the posttranscriptional regulatory sequences of SEQ ID NOS: 1-4 could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on

> the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the person skilled in the art could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on regulatory, sequences yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, a person of skill in the art would not recognize from the disclosure that Applicant was in possession of the genus of DNA sequences containing numerous nucleotides comprising functional portions or fragments of SEQ ID NOS: 1-4 that retain posttranscriptional regulatory activity. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of numerous nucleotides described as functional portions or fragments SEQ ID NOS: 1-4, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 35, 38-39, 43-46, 54-56 and 64-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector comprising a transgene operably linked to at least two distinct posttranscriptional regulatory elements comprising UTR regions selected from WPRE, APP, tau and TH elements suitable for

transgene delivery to mammalian cells, and methods for expressing a transgene in mammalian cells *in vitro*, using said vector; does not reasonably provide an enablement for said vectors as a gene therapy composition for treating human disease that include retinal degenerative disease, or methods comprising expressing a transgene encoded by said vectors in fibroblasts and neuronal cells *in vivo*, as broadly claimed.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

The claims encompass vectors for transgene delivery in mammalian cells, comprising numerous posttranscriptional regulatory elements that may be used in a multitude of combinations to increase mRNA stability or transgene expression in mammalian cells. The claims further encompass said vectors as gene therapy vehicles for treatment of human disease (claims 54-56).

The instant specification discloses that the vectors of the present invention may be o f various types and origins, such as a plasmid, a recombinant virus, a cosmid, an

artificial chromosome, an episome etc. that are able to infect or transfect mammalian cells *in vivo* (first paragraph, p. 11). The specification further describes the use of said vectors or recombinant cells comprising said vectors for the manufacture of a medicament for treating a human disease, in particular a neurodegenerative disease (third paragraph, p. 12). Therefore, when given their broadest reasonable interpretation in light of the teachings of the instant disclosure, the claims further embrace methods of expressing transgenes using numerous vector constructs for the therapy of human disease (claims 64-67).

The Amount Of Direction Or Guidance Presented And Working Examples

The specification while disclosing four distinct posttranscriptional regulatory elements that may be used in different combinations to enhance the expression of a reporter transgene in various cell lines *in vitro*, does not provide adequate representations of functional portions or fragments of the UTR elements. The specification describes the construction of plasmid vectors containing different combinations of the WPRE, tau, APP and TH UTR elements to increase the expression of the luciferase reporter gene and GDNF transgene (p. 18); and the transient transfection of cell lines *in vitro* with said constructs (p. 19).

The results following the transfection of the various plasmid vector constructs show that certain combinations of the four posttranscriptional regulatory elements resulted in enhanced transgene expression in different cell lines (Figs. 1-8, pp. 20-28), concluding that the results provide important information regarding the construction of vectors for gene therapy and study of gene function (last paragraph, p. 28).

The specification further describes a number of viral vectors that include adenovirus, adeno-associated virus, retrovirus and lentiviruses for transfection of mammalian cells *in vitro* or *in vivo* (p. 11). However, vectors and methods directed to the treatment of human disease require an enabling disclosure. The specification is silent on the production and subsequent delivery of vectors containing functional portions or fragments of various combinations of posttranscriptional regulatory elements, to any subjects *in vivo*, or the amelioration of any disease condition following such delivery.

Therefore, it would require further undue experimentation to determine the sequences representing functional portions and fragments of any UTR region of a eukaryotic mRNA or for any of the four regulatory elements disclosed, and to demonstrate the combinations of these elements in numerous vectors for transfer and expression of a desired transgene for treating a human disease, as instantly claimed. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses plasmid vectors containing various combinations of four posttranscriptional regulatory elements that increase transgene expression in cell lines *in vitro*.

In view of the lack of teachings or guidance provided by the specification with regard to delivery of a desired transgene to any tissue of a subject by any vector, and the lack of teachings or guidance provided by the disclosure with regard to functional portions or fragments of regulatory elements in a vector, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The State Of The Prior Art, And The Unpredictability Of The Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art regarding the construction of vectors with enhanced gene expression as potential gene transfer systems for neurodegenerative disease is effectively summarized by the reference of Deglon et al. (Hum. Gene Ther. 11:179-190; 2000).

Deglon et al. describe self-inactivating lentiviral vectors carrying the human GDNF transgene as a candidate for delivery and potential treatment for neurodegenerative disease (Abstract). The authors state: "Numerous studies have established the neuroprotective and/or neurorestorative properties of GDNF on

dopaminergic neurons. However, an appropriate mode of administration is required to further establish its potential clinical use because of the presence of the blood-brain barrier and the broad spectrum of activities of GDNF on peripheral and central nervous neurons." (first column, p. 188). They conclude: "The clinical application of such vectors will, however, require the careful assessment of the biosafety in animal models, the development of sensitive assays for the detection of replication-competent retroviruses, as well as the developmental of a packaging cell line to produce validated batches of vectors." (last paragraph, p. 188). Therefore, additional experiments are required to enable the therapeutic application of these vectors, as there are a number of parameters that remain unpredictable.

With regard to nucleic acid vectors for applications that include gene therapy, the prior art effectively addresses the limitations, drawbacks and unpredictability of said vectors. For example, Thomas et al. (Nature Rev./Genet. 4: 346-358; 2003) state: "The science of gene therapy has a turbulent history. Initially perceived as a revolutionary new technology with the promise to cure almost any disease-provided that we understand its genetic or molecular basis-enthusiasm rapidly waned as clinical trial after clinical trial failed to show efficacy. The stumbling block seemed to be the vehicles that were used to deliver the therapeutic genes to the target tissue; early recombinant viral vectors were inefficient, failed to persist in host cells and transgene expression was typically short lived. Then, in 1999, an adverse patient reaction to an adenovirus vector during a clinical safety trial led to the realization that the failure to understand the biology of vector interactions with the human immune system could have fatal consequences. The year 2000 brought the first gene-therapy success in which three children were cured of a fatal immunodeficiency disorder, but this therapy has subsequently caused a leukemia-like disease in 2 of the 11 patients who have been treated" (column 1, p. 346). Thomas et al. further state: "The ability to accurately predict vector-related side effects at a particular dose is confounded in human studies by the degree of variability between immune responses in different individuals". ..."T-cell responses can still be elicited against the expressed transgene product, particularly if the vectors transduce cells that are robust for antigen presentation, including dendritic cells. The route of vector administration might

affect the degree to which dendritic cells are transduced; route of administration has a profound effect on the development of T-cell responses to transgenes that are expressed from AAV vectors. Pre-existing humoral immunity to the parental wild-type viruses is another obstacle that affects all classes of viral vector. Circulating virus-neutralizing antibodies can preclude efficient transduction with the viral vector" (column 2, p. 353, last two paragraphs). In specifically addressing the problems associated with the route of administration of AAV vectors, Brockstedt et al. (Clinical Immunol. 92:67-75; 1999), observed that "mice injected with a single dose of rAAV developed humoral immunity to the encoded transgene and AAV proteins, regardless of the route of administration" (second column, , p. 73). In addressing the CTL response, the authors further observed: "the strength of the CTL response correlated with the route of administration" (first column, last paragraph, p. 68). The highest CTL responses included intravenous administration of AAV (panel C, Fig. 2, p. 71). Therefore, the prior art teaches that the utility of gene transfer vectors for therapy of human disease is unpredictable.

Regarding the level of skill, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation due to the immaturity of the art, its complexity, and its unpredictability, as shown by the other factors.

The claims of the instant application are drawn to methods of treating human disease using numerous vectors comprising posttranscriptional regulatory elements and transgenes of interest, not apparent from the disclosure of the invention. Therefore, in light of the guidance provided by the disclosure of the application and the unpredictability of the art, it would require undue experimentation by the skilled Artisan to carry out the experiments required to demonstrate that a variety of transgene delivery vectors comprising combinations of posttranscriptional regulatory elements and transgenes of interest may be used to deliver by any means of administration to a subject for the treatment of human disease. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is enabled for the method of delivery to a subject of numerous vectors comprising any sequence of interest for gene therapy, as claimed in the instant application, given the detail of the disclosure provided by Applicant, in view of the knowledge in the prior art. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Analysis And Summary

Applicant is therefore enabled for a vector comprising a transgene operably linked to at least two distinct posttranscriptional regulatory elements comprising UTR regions selected from WPRE, APP, tau and TH elements suitable for transgene delivery to mammalian cells, and methods for expressing a transgene in mammalian cells *in vitro*, using said vector. In the instant case, and for the specific reasons cited above, in a highly unpredictable art where the generation of a safe viral vectors for transgene delivery to any tissue by through any route of administration, that include systemic, is yet to be achieved, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification regarding the generation of such vectors comprising numerous functional portions or fragments of posttranscriptional regulatory sequences, it is the position of the examiner that it would require undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-36 47-51, 53-55, 57-58, and 60-63 are rejected under 35 USC § 102(a) by Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001).

Barry et al. teach lentiviral vectors for provirus integration into nondividing mammalian cells, wherein the incorporation of two distinct posttranscriptional regulatory elements, namely a central polypurine tract (cPPT) and a human hepatitis virus posttranscriptional regulatory element (PRE) that provide increased transgene expression. Barry et al. further teach the use of CMV and RSV promoters in their vectors (Fig. 1; limitation of claim 47), to control the expression of the GFP marker gene (Abstract, limitation of claim 48). For viral vector production and virus packaging, plasmid constructs carrying the pRRL lentiviral vectors are co-transfected into human 293T cells with an HIV gag/pol packaging construct, hence the lentiviral vectors are replication defective (first column, p. 1105, limitations of claims 50-51 and 53-54). Additionally, the foregoing transfection is plasmid mediated (limitation of claim 63).

Barry et al. also teach the virus mediated infection of HeLa cells *in vitro* for determination of lentivirus vector titers (second column, p. 1105). Further, transgene expression as determined by GFP expression was increased over the sum of the components alone, suggesting a synergistic effect (Abstract and Fig. 1; limitation of claim 57). The lentiviral vectors of Barry et al. additionally contain polyadenylation signals in their LTR regions (depicted by $(A)_n$ in Fig. 1, p. 1104), that constitute a third posttranscriptional regulatory element, well established to confer increased mRNA stability (limitation of claim 36). Barry et al. describe the potential use of their vector system for preclinical animal studies (second column, p. 1104) and therapeutic applications (second column, p. 1107). Therefore, the lentiviral vectors are intended for use in the treatment of human disease (limitation of claim 55).

Therefore, each and every limitation of claims 35-36 47-51, 53-55, 57-58, and 60-63 is anticipated by Barry et al., absent evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 35, 37-38 and 46 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538; of record).

Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression as outlined *supra*. However, Barry et al. do not describe the inclusion of a UTR from a eukaryotic mRNA in their vector.

Paulding et al. describe a 27-base-long pyrimidine-rich sequence within the tyrosine hydroxylase (TH) mRNA 3' untranslated region (UTR) that confers mRNA stability in catechollaminergic cells, and further show that the TH UTR element contains a hypoxia induced protein binding site in PC12 cells (Abstract and first column, p. 2532). The sequence described by Paulding et al. represents a functional fragment of SEQ ID NO: 4.

Barry et al. state that posttranscriptional regulatory elements (PRE) stabilize virus vector mRNA and lead to increased transgene expression (first paragraph, p. 1104). Additionally stating: "Therefore, we investigated the incorporation of cPPT and PRE elements into lentivirus vectors to achieve increases in transduction efficiency and gene

expression that would permit reduced levels of both virus production and administration in preclinical animal studies. We compared the effects of the cPPT and PRE elements individually and together on transduction efficiency and gene expression, using a third generation lentiviral vector pRRL encoding enhanced green fluorescent protein (GFP) and erythropoietin (EPO), a secreted growth factor." (second column, p. 1104). Therefore, given the goal of constructing efficient lentiviral vectors for gene transfer that contain two or more posttranscriptional regulatory elements, and the observation that said elements act to increase transgene expression in combination and in synergistic fashion, Barry et al. provide the motivation to substitute or combine additional posttranscriptional regulatory elements with their vector, as a matter of design choice, for further improving transgene expression.

Therefore, a person of ordinary skill in the art, would have been motivated to combine the regulatory elements described by Barry et al., and the TH regulatory element of Paulding et al., thus resulting in the vector of the instantly claimed invention with a reasonable expectation of success. It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine or substitute the regulatory elements described by Barry et al. with the TH regulatory element of Paulding et al. because the combination of the regulatory elements would likely result in synergistic enhancement of transgene expression.

Claims 39 and 43 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538; of record), as applied to claims 35, 37-38 and 46 above, and further in view of Ramezani et al. (Mol. Ther. 2:458-469; 2000; of record).

Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression as outlined *supra*. Barry et al. do not describe the inclusion of a WPRE element in their vector, but provide the motivation to combine or substitute different PREs in their vector system.

Ramezani et al. describe the inclusion of the WPRE element to enhance lentiviral transgene expression in several self-inactivating vectors containing the GFP reporter transgene (Abstract). The authors discovered that the WPRE element stimulated GFP expression in several vectors up to 3-fold, when compared to vectors wherein the WPRE element was removed. The sequence described by Ramezani et al. represents a functional fragment of SEQ ID NO: 1.

Therefore, a person of ordinary skill in the art, would have been motivated to combine separate regulatory elements as described by Barry et al. (*supra*), to include the WPRE regulatory element of Ramezani et al., thus resulting in the vector of the instantly claimed invention, because the combination of the regulatory elements would likely result in the synergistic enhancement of transgene expression. It would have been obvious for a person of ordinary skill in the art at the time of the instant invention, to combine the aforementioned two elements in lentiviral vectors with a reasonable expectation of success, because the resulting increased mRNA stability would allow for the enhanced expression of a desired transgene.

Claims 40, 44, and 64-65 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538; of record) and Ramezani et al. (Mol. Ther. 2:458-469; 2000; of record), as applied to claims 35, 37-39, 43 and 46 above, and further in view of Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999; of record).

Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression as outlined *supra*. Ramezani et al. describe the inclusion of the WPRE element to enhance lentiviral transgene expression, as previously described. Ramezani et al. further describe the goal of developing their lentiviral vectors for human gene therapy and *in vivo* delivery to tissues that include the retina and the brain (first column, p. 458). While, neither Barry et al. nor Ramezani et al. describe the inclusion of an APP 5' UTR element in their vector, Barry et al. provide the motivation to combine or substitute different PREs in their vector system.

Rogers et al. describe a 90 nucleotide sequence in the amyloid precursor protein (APP) gene 5' untranslated region (5'UTR) that enhance the translation of a transgene mRNA product (Abstract). The APP sequence described by Rogers et al. is a functional fragment of SEQ ID NO: 2. Rogers et al. further note that induction of APP mRNA expression was not achieved by microglial IL-1 stimulation in glial cells (first column, p. 6422). The teachings of Barry et al. provide the motivation to combine different PREs into lentiviral vectors, as previously described. The teachings of Ramezani et al. regarding gene therapy of the brain, provide the motivation for application of the lentiviral vector system for delivery of transgenes to neuronal cells.

Therefore, a person of ordinary skill in the art, at the time of the instant invention would have been motivated to combine separate regulatory elements as described by Barry et al. (*supra*), to include the WPRE regulatory element of Ramezani et al., and the APP element of Rogers et al., thus resulting in the vector of the instantly claimed invention with a reasonable expectation of success, because the combination of the regulatory elements would likely result in the synergistic enhancement of transgene expression. A person of ordinary skill in the art, at the time of the instant invention, having combined the WPRE and APP elements would further be motivated to utilize the resulting vector for introduction of transgenes of interest in glial cells for potential therapy, because the APP element alone was shown not to increase mRNA stability in glial cells. Therefore a person of ordinary skill in the art, having expressed the lentiviral vector carrying the aforementioned two elements in glial cells would have a reasonable expectation of success, because, the increased mRNA stability would allow for the enhanced expression of a desired transgene in a glial cell. As the expression of constructs and their effects on gene expression was analyzed in a variety of cell lines of different lineages, it would have been obvious for a person of ordinary skill in the art to have included fibroblasts, routinely used in the art as a host cell for determining the posttranscriptional regulatory effects of the aforementioned elements, with a reasonable expectation of success, as fibroblasts cells are routinely used in the study of gene expression.

Claims 41-42, 45 and 66-67 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view Paulding et al. (J. Biol. Chem. 274:2532-2538; of record) and Ramezani et al. (Mol. Ther. 2:458-469; 2000; of record), and Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999; of record), as applied to claims 35, 37-40, 43-44, 46, and 64-65 above, and further in view of Aronov et al. (J. Mol. Nerurosci., 12:131-145; 1999; of record).

Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression as outlined *supra*. Paulding et al. describe a 27-base-long pyrimidine-rich sequence within the tyrosine hydroxylase (TH) mRNA 3' untranslated region (UTR) that confers mRNA stability (see above). Ramezani et al. describe the inclusion of the WPRE element to enhance lentiviral transgene expression, as previously described, and Rogers et al. increased mRNA translation mediated by the APP 5' UTR element, and discussed the expression of APP mRNA following IL-1 induction in glial cells (*supra*). While, neither Barry et al., Paulding et al., Ramezani et al. or Rogers et al. describe the inclusion of a tau 3' UTR element in their vector, Barry et al. provide the motivation to combine or substitute different PREs in their vector system.

Aronov et al. describe a 240 bp (H fragment) of the tau 3'UTR that can stabilize c-fos transgene and tau mRNAs (Abstract). The sequence described by Aronov et al. is a functional fragment of SEQ ID NO: 3.

Therefore, a person of ordinary skill in the art, would have been motivated to combine separate regulatory elements as described by Barry et al., to include the TH 3'UTR element of Paulding et al., the WPRE regulatory element of Ramezani et al., the APP element of Rogers et al., and the tau 3'UTR region of Aronov et al., thus resulting in the vector of the instantly claimed invention with a reasonable expectation of success, because the combination of the regulatory elements would likely result in the synergistic enhancement of transgene expression.

The teachings of Ramezani et al. regarding gene therapy of the brain, provide the motivation for application of the lentiviral vector system for delivery of transgenes to neuronal cells.

A person of ordinary skill in the art, having combined the WPRE, APP, TH and tau elements would further be motivated to utilize the resulting vector for introduction of transgenes of interest in neuronal cells for potential therapy, because the APP element alone was shown not to increase mRNA stability in glial cells. Therefore a person of ordinary skill in the art at the time of the instant invention, having expressed the lentiviral vector carrying the aforementioned three elements in neural cells would have a reasonable expectation of success, because, the increased mRNA stability would allow for the enhanced expression of a desired transgene in a neuronal cell.

Claims 52, 56 and 59 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), as applied to claims 35, 37-38 and 46 above, in view of Chang et al. (Curr. Gene Ther. 2:237-251; 2001).

Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression as outlined *supra*. However, Barry et al. do not describe a neurotrophic factor transgene in their vector. However, the lentivirus vector of Barry et al. is designed with GFP as an exemplary transgene, and improved tropism for the transfer of any gene of interest into tissues that include nondividing cells (Intro., p. 1103). Thereby providing the motivation to include any gene of interest in the lentivirus vector.

Chang et al. review the state of the art with regard to the utility of lentiviral vectors for gene therapy (entire article). Chang et al. describe examples of *in vivo* lentiviral transduction studies (Table 3, p. 245), with specific reference to lentiviral vectors carrying the glial cell-derived neurotrophic factor (GDNF) gene introduced into monkey brain cells for the correction of Parkinson disease-like symptoms (first column, p. 245). Additional examples of transgenes used include the PDEβ gene for transduction of the retina (Table 3, p. 245) and the rescue of photoreceptor degeneration (Takahashi reference, p. 250), thus providing the motivation to include these genes as therapeutic genes in improved lentiviral vectors.

Therefore, a person of ordinary skill in the art, would have been motivated to include in the lentiviral vector of Barry et al., a neurotrophic transgene or a PDEβ gene, as described by Chang et al., thus resulting in the vector of the instantly claimed invention. A person of ordinary skill in the art at the time of the instant invention, would have a reasonable expectation of success by including in the lentiviral vector a transgene encoding a neurotrophic factor or a photoreceptor, because the combination of the neurotrophic and photoreceptor transgenes and lentivirus vector would enable the transfer and expression of the transgenes in neural or retinal cells, with increased transgene expression, for potential therapy.

Hence, the claimed invention a whole is *prima facie* obvious, absent evidence to the contrary.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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